

MOLECULAR AND DEVELOPMENTAL BIOLOGY OF CARTILAGE

a) Outline

Much progress has been recently made in several areas that have a strong impact on our understanding of chondrocyte differentiation and cartilage formation. Recent studies include discoveries of new retinoic acid receptors, of new homeodomain containing proteins, and other transcription factors which are expressed in differentiating chondrocytes during embryonic development. Some of the genes coding for these proteins have been mutated in mice by the techniques of homologous recombination in embryonic stem cells. These mutations cause abnormal phenotypes which mostly affect the formation and shape of the skeleton. Other studies have identified novel cytokines (bone morphogenetic proteins, BMP) which are new members of the transforming growth factor- β (TGF- β) superfamily. These cytokines have been shown to possess the ability to trigger cartilage formation and endochondral bone formation in vivo. Mutations in one of these BMPs have been identified to cause skeletal anomalies in mice. The function of a number of structural components of the cartilage extracellular matrix has also been studied by generating transgenic mice which carry mutations in the genes for these proteins. Mutations in the same genes have been also identified in human genetic diseases and correlated with abnormal function or development of cartilage.

Hitherto, there has not been a meeting bringing together investigators with active programs in these different areas of research. We feel that a meeting on the molecular and developmental biology of cartilage is timely because much progress is being made in different but converging areas. Such a meeting will greatly foster additional progress which should in turn lead to a much better understanding of the molecular mechanisms which control: (a) chondrocyte differentiation during embryonic development; (b) the formation of sclerotomes; (c) the development of limbs and other skeletal structures; (d) the role of novel cytokines in these processes; and (e) the unique functions of individual components of the extracellular matrix. More generally, this information will provide new insights on how these various components interact with each other and with cells, and how they influence the chondrocytic phenotypes. Studies to elucidate a number of genetic diseases in humans which affect cartilage function will also benefit from such an interdisciplinary meeting. Finally, the convergence of different methodological approaches should lead to a much broader and in depth understanding of the role of cartilage during development and in diseased states. We strongly believe that the field of the molecular and developmental biology of cartilage is an emerging and exciting area of research to which a large group of scientists from different disciplines can make a substantial contribution.

b) Proposed Program

DAY 1:

Session I: (8:30 a.m. - 11:45 a.m.)

RETINOIC ACID AND OTHER INDUCERS OF SKELETOGENESIS

Chair: Benoit de Crombrughe

8:30-8:45 a.m.	INTRODUCTION: Benoit de Crombrughe	
8:45-9:15 a.m.	Gregor Eichele Baylor College of Medicine (Houston)	Role of retinoic acid in early development
9:15-9:45 a.m.	Pierre Chambon Institut de Chimie Biologique (Strasbourg)	Function of retinoic receptor
9:45-10:15 a.m.	Gail Martin University of California School of Medicine (San Francisco)	Growth factor and limb development
10:15-10:45 a.m.	COFFEE BREAK	
10:45-11:15 a.m.	Rudolph Jaenisch Whitehead Institute (Boston)	Mutations in helix-loop-helix protein which affect skeletal development
11:15-11:45 a.m.	Shirley Tickle University College and Middlesex School of Medicine (London)	Chondrogenesis in limb development
11:45-1:45 p.m.	LUNCH	

Session II: (1:45 p.m. - 5:00 p.m.)

ROLE OF HOMEBOXES IN SKELETOGENESIS

Chair: Pierre Chambon

1:45-2:00 p.m.	INTRODUCTION: Pierre Chambon	
2:00-2:30 p.m.	Peter Gruss University of Heidelberg	Role of pax genes in formation of the skeleton
2:30-3:00 p.m.	Rudi Balling Max Delbrück Laboratorium (Cologne)	Pax genes in development
3:00-3:30 p.m.	COFFEE BREAK	
3:30-4:00 p.m.	Alan Bradley Baylor College of Medicine (Houston)	Targeted inactivation of homeobox genes
4:00-4:30 p.m.	Benoit de Crombrughe MD Anderson Cancer Center (Houston)	Role of Cart 1 in the chondrogenesis determination pathway
4:30-5:00 p.m.	Robert Maxson University of Southern California (Los Angeles)	Evolution and function of the msx-2 homeobox gene.

DAY 2:**Session III: (8:30 a.m. - 11:45 a.m.)****CYTOKINES AND ONCOGENES IN THE FORMATION OF THE SKELETON***Chair: A. Hari Reddi*

8:30-8:45 a.m.	INTRODUCTION: Hari Reddi	
8:45-9:15 a.m.	Elizabeth Wang Genetics Institute, Inc. (Boston)	Biology of BMPs
9:15-9:45 a.m.	Brigid Hogan Vanderbilt University (Nashville)	Embryology of BMPs
9:45-10:15 a.m.	Karl Heldin Ludwig Institute for Cancer Research Biomedical Centre (Uppsala)	Receptors for BMPs
10:15-10:45 a.m.	COFFEE BREAK	
10:45-11:15 a.m.	Erwin Wagner Research Institute of Molecular Pathology (Vienna)	Effect of oncogenes on skeleton formation
11:15-11:45 a.m.	Hari Reddi John Hopkins Hospital (Baltimore)	Cytokines and skeletal development
11:45-1:45 p.m.	LUNCH	

Session IV: (1:45 p.m. - 5:00 p.m.)**CELL BIOLOGY OF CHONDROCYTES AND THEIR MATRIX***Chair: Bjorn Olsen*

1:45-2:00 p.m.	INTRODUCTION: Bjorn Olsen	
2:00-2:30 p.m.	Dick Heinegard University of Lund	Structure and function of cartilage matrix
2:30-3:00 p.m.	Bjorn Olsen Harvard Medical School (Boston)	Molecular biology of cartilage matrix
3:00-3:30 p.m.	COFFEE BREAK	
3:30-4:00 p.m.	Ranieri Cancedda Istituto Nazionale per la Ricerca sul Cancro (Genova)	Cell biology of cartilage matrix
4:00-4:30 p.m.	Claire Francomano John Hopkins Hospital (Baltimore)	Mutations in chondrodysplasias with metaphysal involvements
4:30-5:00 p.m.	Tomoatsu Kimura Osaka University Medical School	Transgenic model for chondrodysplasias

DAY 3:

Session V: (8:30 a.m. - 11:15 a.m.)

NATURALLY OCCURRING MUTATIONS IN HUMANS AND MICE

Chair: Francesco Ramirez

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| 8:30-8:45 a.m. | INTRODUCTION: Francesco Ramirez | |
| 8:45-9:15 a.m. | William Horton
University of Texas
(Houston) | Human chondrodysplasias |
| 9:15-9:45 a.m. | Francesco Ramirez
Mount Sinai School of Medicine
(New York) | Type II collagenopathies |
| 9:45-10:15 a.m. | COFFEE BREAK | |
| 10:15-10:45 a.m. | Nancy Jenkins
Laboratory of Mammalian Genetics
NCI (Frederick) | Short ear mutation in mice |
| 10:45-11:15 a.m. | Philip Leder
Harvard Medical School
(Boston) | Limb deformity in mice |